Application and Use of Dose Estimating Exposure Model (DEEM) for Route to Route Dose Comparisons After Exposure to Trichloroethylene (TCE)

Cheryl Scot[1], Jerry Blancato[2], Fred Power[3], Jeffrey Fisher[4], Edward Kantor[2]

1 U.S. EPA, National Center for Environmental Assessment, Washington, DC 2 U.S. EPA, National Environmental Research Laboratory, Las Vegas, Nevada 3 Anteon Corporation, Las Vegas, Nevada 4 Armstrong Laboratory, Wright-Patterson AFB, Ohio

1 Abstract

Route to route extrapolations are a crucial step in many risk assessments. Often the doses which result in toxicological end-points in one route must be compared with doses resulting from typical environmental exposures by another route. In this case we used EPA's Dose Estimating Exposure Model (DEEM) to examine the route comparisons of different measures of internal dose after exposure to TCE. DEEM is a physiologically based model architecture for estimating internal tissue doses resulting from actual or simulated exposures. Because of different kinetic rates in the body each possible measure of dose does not have the same quantitative relationship with exposure. Modeling shows that for different choices of internal dose metric the "equivalent" exposures are different. For example, we first chose the dose metric of interest to be the area under the concentration-time curve (AUC) of the metabolite, trichloroacetic acid (TCA). In this case, and with this model set-up, an 8-hour 30 ppm inhalation exposure for five days was equivalent to drinking water intake of 50mg per day for seven days. For other measures of dose the point of equivalent exposure is far different. Thus, information about the mode of action and selection of internal dose metric is crucial before route to route extrapolations can be rationally made.

NOTICE: *The U.S. Environmental Protection Agency (EPA), through its Office of Research and Development, funded this research and approved this abstract as a basis for an oral presentation. The actual presentation has not been peer reviewed by the EPA.*

2 Background

DEEM is a physiologically based pharmacokinetic (PBPK) computer model which mathematically describes and predicts toxicologically relevant doses within the body (e.g. concentration or AUC of exposure chemical(s) and their metabolites within tissues, etc.). The development goal of DEEM is to provide toxicologists, exposure assessors, and risk assessors with an easy to use standard framework for calculating and predicting dose within the body. Exposure profiles are input into DEEM through scenario-based modules or through time-histories. Time-histories are a description of the sequence of exposures to a chemical that an individual receives describing the concentration of the exposure as a function of time. For the simulations given in this presentation, DEEM was specifically configured to simulate trichloroethylene (TCE) pharmacokinetics in the human. In the DEEM representation, TCE is metabolized in the liver to trichloroacetic acid (TCA) and trichloroethanol (TCOH). TCOH is then metabolized to TCOG (glucuronidated TCOH) and dichloroacetic acid (DCA). TCA, DCA, and TCOG are eliminated from the body in urine. TCA and DCA are also eliminated in the liver by a currently unknown mechanism. There were 40 parameters that were obtained from Fisher et al. and the literature on TCE metabolism that were input into DEEM to create the simulations presented here ***(Table 8)***. The model was then tested against data taken from human volunteers (Fisher, et al.) and found to provide excellent correlation between experimentally derived data and model simulations.

3 The Question

Recent data released on the exposure to Trichloroethylene (TCE) of technical workers at a Singapore industrial site became of interest to EPA. Even though the 30 ppm exposure level of TCE fell below the OSHA permissible air concentration of 100 ppm, the fact that this exposure was five days a week for over five years made EPA risk assessors take note. What might be the equivalent exposure by ingestion that would achieve the same dose levels as the 30 ppm inhalation? TCE has a 16,000 mg/kg subcutaneous-mouse LD 50 where as TCE's metabolite, TCA, has a 270 mg/kg subcutaneous LD 50. Since TCA is 60 times more toxic than TCE, TCA was of greater interest to toxicologists and exposure assessors. The question then was what **ingestion exposure** would equate to the Area Under the Curve in blood (AUC, the integration of concentration over time) of TCA from an **inhalation exposure** of 30 ppm TCE. Using DEEM, route to route exposure-to-dose experimental simulations were designed that would answer this question.

4 Initial Experimental Design

We first needed to determine how the AUC of TCA, produced by the ingestion of a fixed daily amount of TCE, would vary as a function of the number of drinks. In typical drinking water, if TCE is present, the amounts normally found are in the 5 to 10 μg/liter range. For our simulation we chose an amount 10 times higher than normal or 0.1 mg/ liter such that our simulated person would consume 2 liters of water a day or an accumulated daily dose of 0.2 mg. The volume of water ingested for a single drink was 2 liters and took .0195 hrs. As the number of drinking episodes was increased, the volume and time were reduced accordingly such that for the 13 drink episode, the time of each drink was .0015 hrs (1.2 minutes) and the volume was .154 liters. TCE was ingested in a single drink, four drinks, seven drinks and 13 drinks over a 12 hour period for a varying number of days (depending on the length of drinking time) and the results were compared.

5 Initial Results

As can be seen from the plots of ***Graphs 9***, it was found that the distribution of the total daily ingestion of TCE from a single dose or many doses had no discernible difference in the concentrations and AUC for TCA in the blood. The peak TCE and TCOH concentrations in blood are greatly increased when moving to a smaller number of episodes, but the tails of these curves were the same. In addition the AUC's for TCE and TCOH were also very similar and the amount of TCA and TCOG in the urine remain unchanged. This indicated that the number of drinks made very little difference as long as the amount of TCE delivered remained the same over the same 24 hour period. This was attributed to TCE and TCOH metabolizing quickly, and the TCA clearance being very slow.

6 Revised Experimental Design

With the information garnered above, a simulation was designed to determine what daily ingested dose of TCE equated to a similar level of TCA in blood from inhaling 30 ppm TCE. It was decided that the simulation should run long enough such that the TCA AUC levels in blood would stabilize. It was thought that twelve weeks would probably be sufficient for this purpose; this time period, however, presented a problem. The shorter the simulated time step interval between model calculations the longer the model will be required to run, and each time step should be at least be half as small as the shortest time event being monitored. If a drink were to last 1.2 minutes (as in the 13 drink episode) then the time step would have to be 0.6 minutes. In DEEM a time step of 0.6 minutes for 12 weeks would require the model to physically run for days. It was found that an eight hour period of drinking (starting at the 2nd hour and ending at the 10th hour) at 0.025 mg/Hour which would deliver 0.2 mg of TCE, resulted in nearly the same peak TCE concentration in the blood as 13 drinking episodes over a 12 hour period. This continuous eight hour drink simulated with a time step of four hours allowed the 12 week simulation to be run in one and half hours as opposed to days. Model simulations were run for a 12 week daily ingested dose of 400, 200 and 50 mg of TCE and compared with a 30 ppm inhalation of TCE for eight hours a day, five days a week for 12 weeks.

7 Revised Results

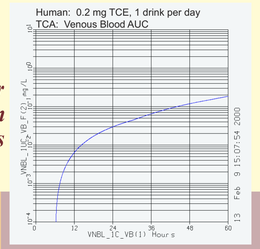
It was determined that an ingested amount of 50 mg/day of TCE for seven days per week resulted in a TCA AUC in Blood level identical to that found from an inhalation of 30 ppm TCE for eight hours a day, five days per week for the three and twelve week exposure ***(Graphs 10)***. In addition the same 50 mg/day dose very closely matched the levels for TCA in the liver for the three week (94%) and twelve week (97%) exposure found from the 30 ppm inhalation ***(Table 11)***.

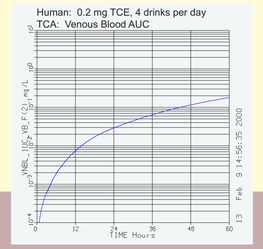
8 Bio-Physiological Parameters for Simulated Person in DEEM

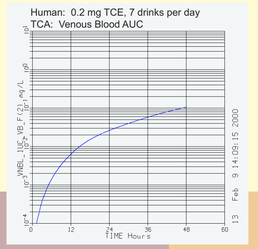
MODEL PARAMETER	MEAN
PARTITION COEFFICIENT	
TCE-FA	52.34
TCE-Kidney	1.08
TCE-Liver	4.85
TCE-Lung-Blood	0.39
TCE-Lung-Air	11.15
TCOH-Liver	0.59
TCA-Liver	0.66
TCA-Kidney	0.66
TCOG-Liver	0.6
TCOG-Kidney	1.4
DCA-Liver	0.8
DCA-Kidney	0.8
SATURABLE METABOLISM	**Mg/Hour**
TCE-TCA-Km	10.8
TCE-TCA-Vmax	6
TCOH-TCOG-Km	160
TCOH-TCOG-Vmax	30
TCOH-DCA-Km	10
TCOH-DCA-Vmax	0.1
Rate Constants	**Per Hour**
Stomach to Portal Blood	3.9
Stomach to Intestine	2.18
Intestine to Portal Blood	0.044

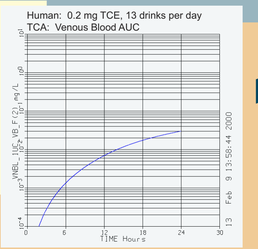
MODEL PARAMETER	MEAN
VOLUME	**Liters**
Body Volume	70
Muscle for Lower Limit	59.462
Muscle for Upper Limit	27.338
Given Fat	14
Kidney	2.8
Liver	1.82
Lung	0.98
Venous Blood	2.1
BLOOD FLOW	**Liter/Hour**
Alveolar Ventilation	450.12
Given Cardiac Output	384.78
Fat	18.46944
Kidney	75.80166
Liver	92.3472
Linear Metabolism	**1/Hour**
TCOH-TCA-Rate-Const	7
Linear Elimination Rate Const.	**1/Hour**
TCA-Urine	0.75
TCA-Liver	0.2
TCOG-Urine	40
DCA-Urine	0.00795
DCA-Liver	7.0873

9 Plots of the Area Under the Curve of TCA in Venous Blood for One, Four, Seven and Thirteen Drinks a Day for Five Days

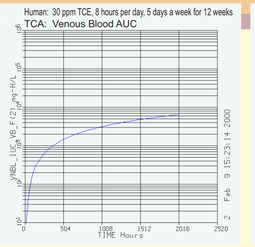


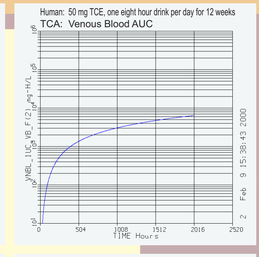


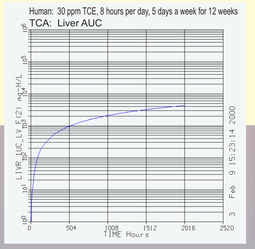


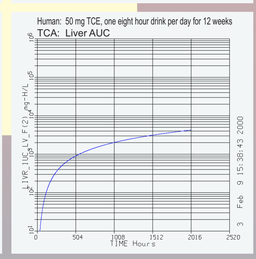


10 Plots of the Area Under the Curve of TCA in Venous Blood and Liver Derived from a 50 mg Ingested Daily Dose and a 30 mg Inhalation Dose









11 Table of TCA AUC in Blood and Liver from a 30 ppm TCE Inhalation and for 50, 200, and 400 mg/day TCE Ingestion Dose

Exposure		TCA AUC in Blood (mg-H/Liter)	TCA AUC in the Liver (mg-H/Liter)
Inhaled TCE 30 ppm	3wk	1500.0	960.0
	12wk	6500.0	4300.0
Ingest 50 mg/day	3wk	1500.0	900.0
	12wk	6500.0	4150.0
Ingest 200 mg/day	3wk	5500.0	3700.0
	12wk	27,000.0	18,000.0
Ingest 400 mg/day	3wk	11,000.0	7000.0
	12wk	50,000.0	32000.0

12 Conclusions

The total daily dose of a chemical at low concentrations may be the deciding factor when assessing toxicological affects rather than the number of times a day that a person is exposed to that chemical. For chemicals that are not immediately metabolized and accumulate in the body the relevant biological doses of specific doses by inhalation and ingestion may be equivalent. The validity of these conclusions will be further tested against simulations and experimental data for other chemicals and over a range of different individuals and body types found in the general population.

169HERB00.db